REMARKS/ARGUMENTS

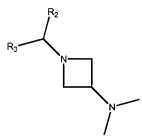
The office action of August 22, 2008 has been carefully reviewed and these remarks are responsive thereto. Reconsideration and allowance of the instant application are respectfully requested. Claims 1-8, 11-17, 19-21 remain pending.

Applicants appreciate the indication in the Advisory Action mailed January 13, 2009 that the minor amendment to claims 12 and 20 to correct very minor grammatical errors will be entered. No new issues or new matter are raised by these amendments. Applicants address the article newly cited in the Advisory Action in the remarks below.

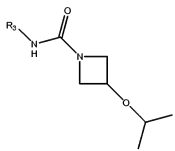
Claims 1-8, 11-17, 19-21 remain rejected under 35 USC 103(a) over Adams et al. (US 6,403,574) in view of Achard et al. (US 2002/0019383). This rejection is respectfully traversed.

Below is provided a comparison of the compounds disclosed by Achard and the compounds disclosed by Adams.

Achard:



Adams



It is very clear that the substituents attached to the N in each ring are different. Achard requires a $-CR_2R_3$ and Adams requires a $-C(=O)-NHR_3$. Achard does not allow a carboxyl group to be attached to the N. It is also clear that the substituents attached to the C in each ring are very different. Achard requires a -N- and Adams requires a -O-.

The only commonality between Adams and Achard is a four-membered ring having two substituents. However, each of the two substituents is different and the possible substituents do not over lap with each other. "Sufficiently close" is not "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the

way the claimed new invention does." Moreover, as demonstrated above, the compounds of Adams and Achard are not so "sufficiently close" that one skilled in the art would have modified Adams in view of Achard to arrive at the instant claims.

The present inventors discovered that compounds similar to those disclosed in Adams are suitable for treatment of obesity, excessive food intake, and smoking craving. **(Note:** these are not disorders of the central nervous system.) Adams does not teach or suggest the use of its disclosed compounds for the treatment of obesity, excessive food intake, and smoking craving. Instead, Adams is directed to the treatment of central nervous system (CNS) disorders such as anxiety and epilepsy. See column 4, line 55, to column 5, line 48.

The Office Action recognizes that Adams does not teach the claimed compounds for the treatment of obesity, excessive food intake, and smoking craving. Instead, the Office Action selects Archard which is directed to significantly different compounds.

Achard provides a laundry list of possible treatments using its disclosed compounds. Although Achard mentions all these possible treatments, nowhere is data provided that any of the compounds are actually effective for any of the disorders listed. Achard simply states that the disclosed compounds are CB1-receptor antagonists and then suggests in paragraph [0084] that such antagonists could be used in the "treatment and prevention of disorders affecting the central nervous system, the immune system, the cardiovascular or endocrine system, the respiratory system, the gastrointestinal apparatus and reproductive disorders." In paragraph [0085] Achard states:

> Accordingly, these compounds may be used for the treatment or prevention of psychoses including schizophrenia, anxiety disorders, depression, epilepsy, neurodegeneration, cerebellar and spinocerebellar disorders, cognitive disorders, cranial trauma, panic attacks, peripheral neuropathies, glaucomas, migraine, Parkinson's disease, Alzheimer's disease, Huntington's chorea, Raynaud's syndrome, tremor, obsessive-compulsive disorder, senile dementia, thymic disorders, Tourette's syndrome, tardive dyskinesia, bipolar disorders, cancers, movement disorders induced by medicaments, dystonia, endotoxemic shocks, hemorrhagic shocks, hypotension, insomnia, immunological diseases, multiple sclerosis, vomiting, asthma, appetite disorders (bulimia, anorexia), obesity, memory disorders, in weaning from chronic treatments and alcohol or drug abuse (opioids, barbiturates, cannabis, cocaine, amphetamine, phencyclide, hallucinogens, benzodiazepines for example), as analgesics or potentiators of the analgesic activity of the narcotic and nonnarcotic drugs. They may also be used for the treatment or prevention of intestinal transit.

Thus Achard appears to suggest his compounds are a cure all for all types of

disorders. There is no evidence that any of the compounds are actually effective for any of the listed treatments. Thus, it is speculative at best whether the compounds of Achard are actually effective for the treatments listed. Certainly one skilled in the art viewing the laundry list of potential treatments for the Achard compounds would have no reason to expect that the compounds of Adams would be effective for treatment of obesity, excessive food intake, and smoking craving.

Furthermore, it is well known that modulation of receptors, such as the CB1 receptor, depends on a very close interaction of the tertiary structure and charge properties of the modulator compound with the complex tertiary and charge structure of the receptor sequence. It is too simplistic to say that because both Achard and Adams have an azetidine core with substituents on the nitrogen and 3-carbon, they are expected to have the same CB1 antagonistic activity irrespective of the rather major differences in what those substituents actually are.

As previously noted, Adams does not teach the use of its disclosed compounds for treatment of a disorder selected from the group consisting of obesity, excessive food intake, and smoking as claimed in amended claim 1. Moreover, the use of the disclosed compounds as claimed are not obvious applications of the Adams compounds. The molecular target disclosed in Adams is the GABAa receptor, and modulation of the GABAa receptor is not known in the art to be involved with the claimed disorders. Thus Adams does not suggest that GABAa receptor modulators would be useful for the now-claimed disorders. Achard does not remedy the defects of Adams.

The Advisory Action newly cites an article "Rosmond." This article links a point polymorphism in a gene encoding a subunit of the $GABA_A$ receptor with abdominal obesity. The point polymorphism "might be involved in the dysfunction of the hypothalamic cortisol homeostasis-controlling mechanisms within the central nervous system" (sentence bridging pages 940 and 941). However, the point polymorphism "is not located in a coding region of the ...subunit gene" so "its functional role, if any, is uncertain" (page 941, last paragraph). Further, page 940, column 2, last sentence of first paragraph states "Although a role for GABA in human obesity has not ...been previously described, these studies suggest that GABAergic tonic inhibition may potentially be involved" (emphasis added). The studies referred to are earlier publications relating to rats with altered brain GABAergic mechanisms which contribute to their overeating, the showing the obese Prader-Willi subjects had higher

plasma GABA levels than non-obese controls.

The tentative tone of the Rosmond reference, and the absence from Rosmond of evidence that $GABA_A$ receptor antagonists are capable of treating obesity (abdominal or otherwise) is inconsistent with the Advisory Action's reliance as a starting point for the proposition that the GABA receptor antagonists of Adams would be obviously useful for treatment of obesity. The true position appears to be that there is no general acceptance that $GABA_A$ receptor antagonists are beneficial in the treatment of the conditions now claimed.

As discussed above, the Achard compounds are not "very close" in structural similarity to those of Adams and the present application. Achard (a) does not have an amide moiety attached to the azetidine nitrogen, and (b) does not have the ether link to the ring carbon in position 3 of the azetidine ring. The only similarity between the Achard and Adams compounds seems to be the common possession of an azetidine ring.

As noted in ***Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007)** "While the KSR Court rejected a rigid application of the teaching, suggestion or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination. (emphasis added)" Further in ***Innogenetics, N.V., v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008)** "We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention."

One skilled in the art would not have had any reasonable expectation that the instant compounds were suitable for the treatments as claimed in view of the laundry list of potential treatments listed in Archard for a different compound. Withdrawal of this rejection is requested.

CONCLUSION

If any further fees are required or if an overpayment is made, the Commissioner is authorized to debit or credit our Deposit Account No. 19-0733, accordingly.

All rejections having been addressed, applicants respectfully submit that the instant application is in condition for allowance, and respectfully solicit prompt notification of the same.

Respectfully submitted,

/Susan A. Wolffe/

Date: April 17, 2009

Susan A. Wolffe
Reg. No. 33,568

Banner & Witcoff, Ltd.
1100 13th Street, N.W., Suite 1200
Washington, D.C. 20005-4051
Tel: (202) 824-3000
Fax: (202) 824-3001